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SCHEDULE OF MEETINGS

12-17 March	**Regional Advisory Group on Water Standards, Regional Office for Europe, Geneva**
19-24 March	**Committee on International Quarantine, third session, Geneva**

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NEW EPIDEMIOLOGICAL ASPECTS OF YELLOW FEVER

"Yellow fever is not a disease which has been conquered. It is not a disease which has been eliminated from consideration as a permanent threat. . . . Too many health authorities get alarmed about yellow fever only when it becomes an urban disease, overlooking entirely the fact that, for the jungle populations and for rural workers who have to go into the forest, yellow fever carries the same threat that it previously had for the people in the cities."

With these introductory remarks, Dr Fred Soper, Director of the Pan American Sanitary Bureau, opened an informal conference on yellow fever which was held in Washington, D.C., in December 1954 and of which a detailed account has been published.[1] The conference was attended by yellow-fever specialists from the US Public Health Service, the Divisions of Preventive Medicine of the US Army, Navy, and Air Force, the Rockefeller Foundation, the Gorgas Memorial Institute, the US Department of State, the Carlos Finlay Institute of Bogotá, Colombia, and members of the staff of the Pan American Sanitary Bureau.

The conference was convened for the purpose of reviewing, in general, the trend of yellow fever during recent decades in the Americas and, in particular, the situation created by an epidemic in Trinidad in 1954 and by a wave of infection which has been advancing in Central America since 1948 and which, by 1954, threatened to push farther northward into regions previously free of the disease.

EPIDEMIOLOGICAL PICTURE

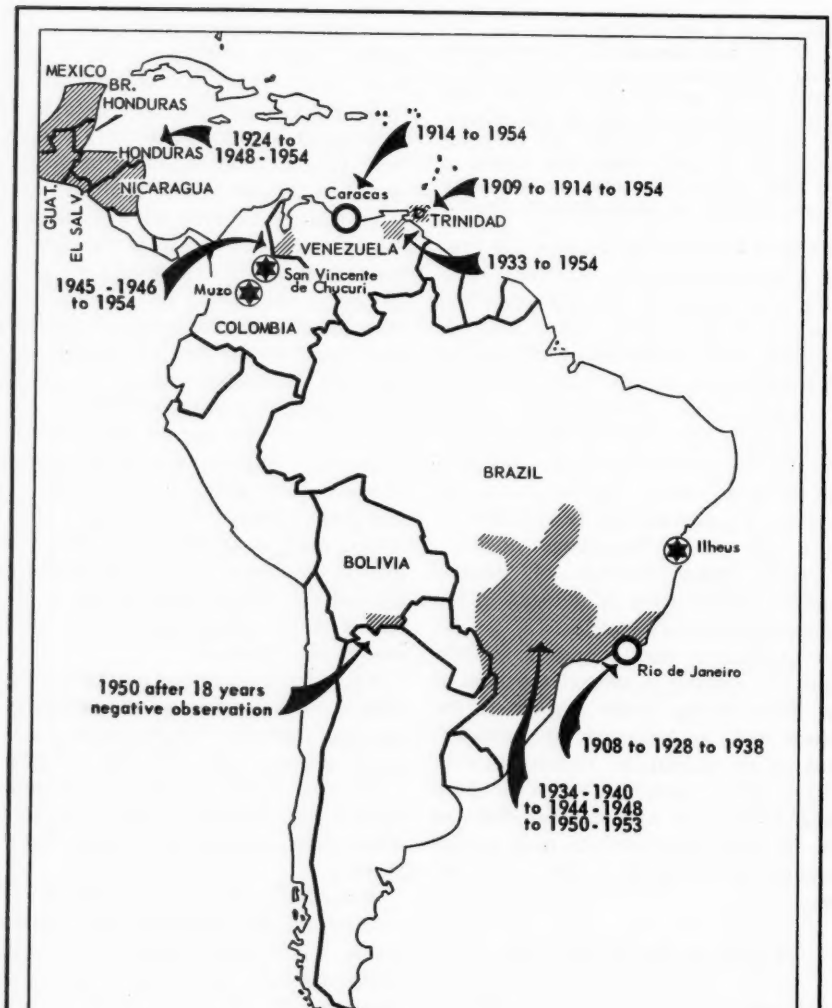
Jungle yellow fever definitely appears at the present time to be a problem which concerns all the countries of the American continent with the exception of the United States, Canada, Uruguay, and Chile. Its epidemiology varies in both time and space. In Brazil, for example, only sporadic cases were noted between 1946 and 1950, while from 1951 to 1953 the infection was widespread in the central and southern portions of the country. In 1954, not a single case had been notified at the time of the conference, but nine proven but non-fatal cases occurred in Pará in December. In Colombia, on the other hand, some cases have been reported every year. In the west of Venezuela, there has been a constant succession of cases in a region where there was an epidemic ten years ago; and, in the east of the country, the disease has reappeared after an absence of 21 years. In Trinidad, no case of yellow fever had been reported for 40 years when the disease made its appearance in 1954; and the infection in Port of Spain with *Aëdes aegypti*-transmitted yellow fever broke a 25-year record of no yellow fever in any maritime port in the Americas.

Fig. 1 shows the cyclical movement of epidemics at various points on the continent and the long intervals—20, 30, or 40 years—between epidemic outbreaks. Fig. 2 shows very clearly the direction taken by an epidemic wave which, starting in 1948 in the Panama Canal Zone, reached the north of Honduras in 1954.

These few examples give some idea of the diversity of the epidemiological aspects of jungle yellow fever. Study of the wave of infection which recently spread through some countries of Central America and which threatened others has revealed the complexity of the biological and climatic factors involved in the propagation of the epidemic outbreaks. Whereas in some cases the wave advanced at a definite speed and in the direction antici-

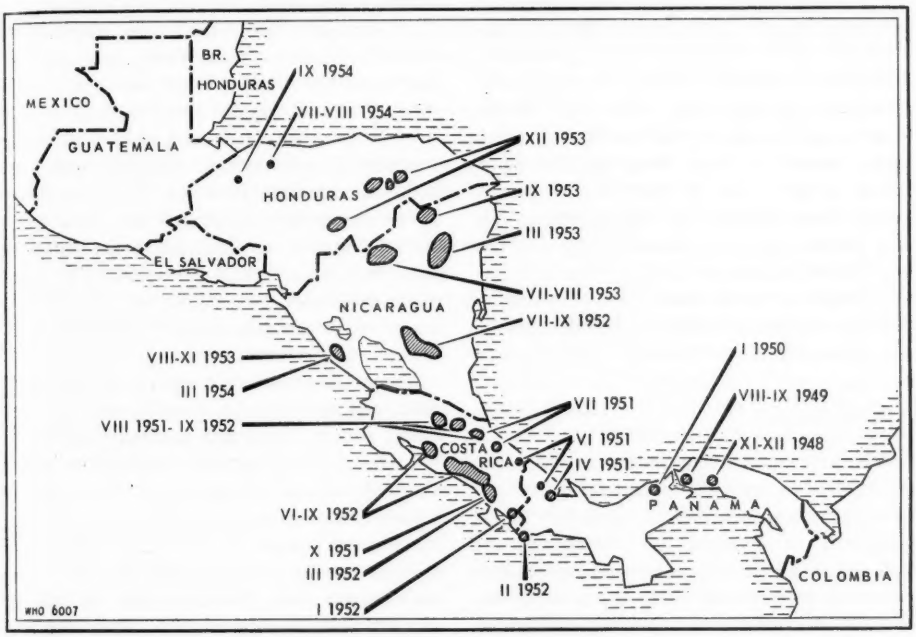
[1] This account, from which the material for the present article has been taken, appeared in English in *Amer. J. trop. Med.*, 1955, **4**, 571-661, and in Spanish in *Bol. Ofic. Sanit. pan-amer.*, 1955, **39**, 1-81.

FIG. 1. INTERVALS BETWEEN APPEARANCE OF YELLOW FEVER IN SPECIFIC AREAS OF LATIN AMERICA



= *Places known to have been constantly infected*

FIG. 2. JUNGLE YELLOW FEVER IN CENTRAL AMERICA, 1948-54



pated, in others it upset all calculations, confronting epidemiologists and biologists with unknowns, which the participants in the yellow-fever conference described and discussed. An attempt is made in the following pages to give a broad outline of these discussions.

The Trinidad episode

The discovery of yellow fever in Trinidad was accidental. In 1953, the Rockefeller Foundation set up a virus laboratory in Trinidad to study the distribution of arthropod-borne viruses other than yellow fever. As part of the investigations, the sera of 700 inhabitants of the island were subjected to neutralization tests with a number of viruses, including yellow fever. Yellow fever antibodies were detected not only in the sera of older people—which was not surprising in view of the fact that there had been an outbreak of yellow fever in 1914—but also in persons between 15 and 20 years of age. This was unexpected, since no outbreak of the disease had been notified since 1914.

Being thus put on their guard, the workers in Trinidad continued their systematic search for virus infections; and, in May 1954, a case of yellow fever was discovered in the Arima hospital, the virus being isolated from the serum of a patient showing only a few mild symptoms.

Hunters who were questioned disclosed that mortality among monkeys had been very high at the beginning of 1954; in some regions the stench from the dead monkeys had been such that the dogs lost the scent they were following and the hunt had had to be abandoned. Examination of monkeys which were

dying or which had died recently (supplied by hunters against recompense) confirmed the presence of yellow fever. The virus was isolated on 12 occasions from *Haemagogus* mosquitos captured on the ground.

Fifteen human cases, with four deaths, were reported during this outbreak. Three cases seemed to have been transmitted by *Aëdes aegypti*; one of them was a case of urban fever detected in Port of Spain. The last known case in a human being was seen in October 1954.

According to the accounts of hunters, an analogous epizootic took a considerable toll among monkeys in 1933-34.

Central America

The first cases in an epidemic which was gradually to advance northward in one principal and a number of secondary waves appeared in Panama in November and December 1948. The next diagnosed case occurred in January 1950, when a farmer died of yellow fever in the Chagres District, west of the Canal on the Atlantic side. This case was part of the principal wave, which swept on across the tropical forest of western Panama in the direction of Costa Rica. In June 1951, a case occurred on the Costa Rican frontier; and then, suddenly, the epidemic burst forth and, from July to October, swept forward towards the north of Costa Rica until it reached the northern plains, where it raged along a 100-mile (160-km) front.

Of 206 persons seen and treated for yellow fever in the Hospital San Juan de Dios in San José, Costa Rica, none contracted the disease at altitudes exceeding about 1640 ft (500 m). This was also the maximum altitude at which monkeys were observed to die of the disease.

While human cases were still occurring in Costa Rica, the virus was moving northward, in the form of an epizootic forerunner; and monkeys east of the great Lake Nicaragua began to succumb.

At the beginning of 1952, a secondary wave started to move northward, and another advanced towards the Pacific coast of north-west Costa Rica, decimating the monkey population as it went. This epizootic onslaught, contrasting sharply with the mildness of the epizootic phase in Barro Colorado in 1949, suggested that there might be an increase in virulence in the virus, at least for the arboreal primates. The main wave continued its course up the Atlantic coast of Nicaragua, roughly following the 1000-ft (300-m) contour.

From then on, the wave of infection advanced up both the Pacific and Atlantic sides, at different speeds and under different climatic and geographical conditions. Along the Atlantic coast, the tropical forests, in which there is heavy rainfall and no well-marked dry season, favour the persistence of the insect vectors throughout the year. On the Pacific side, however, the deciduous tropical forests, which result from the fact that there is a long dry season, would seem to be unfavorable for the survival of mosquitos and, therefore, of the virus. But the virus survived in the area. At the beginning of the rainy season, five to six months later, monkeys began to die precisely where the epizootic had halted when the dry season started.

What acted as the reservoir of virus in the absence of mosquitos, which were not to be found from November to April, during the long dry season? The answer is not known: this is one of the numerous unknowns which the study of the epidemic wave in Central America disclosed. And it shows the danger of prophesying from observations in one place what will happen in other apparently similar places.

The last case of jungle yellow fever in Honduras was reported in September 1954, on the edge of the Ulua Valley. This valley,

which is deforested and is now banana land or swamp land, may perhaps form a barrier against the advance of yellow fever. On the other hand, there is a strip of woodland which may afford a bridge for the virus to cross the valley and make its way into Guatemala, and then southern Mexico.[2]

Is Central America at present experiencing a passing wave of infection which will disappear with the immunization or destruction of susceptible animals, or can it become a permanent reservoir of yellow fever like those existing in certain parts of Colombia? Only long-term observations can supply the answer to this question. Further, even if this wave now halts at Honduras and does not pass on to Guatemala and Mexico, there is no guarantee that the same will be true of the next outbreak, since the epidemiology depends to a great extent on climatic and other factors which govern the abundance of the vector arthropods and vertebrate hosts.

A study carried out over a five-year period at Pacora, Panama, where the first cases of yellow fever were diagnosed in 1948, has revealed considerable cyclical fluctuations in the density of canopy mosquitos: the population of *Haemagogus spegazzinii falco* may be much more dense in a particular month of a particular year than in the same month of another year. In 1949 and 1950 a great and apparently unusual abundance of these mosquitos, caused by optimum rainfall, coincided with the spread of yellow fever virus from the probable reservoir of the virus in eastern Panama. By this means the virus was able to cross the Canal Zone into western Panama.

BIOLOGICAL PROBLEMS

Jungle yellow fever is entering new geographical areas where the arthropod and mammal faunae—and therefore the transmission cycle of the extra human reservoir—are different from those in countries where the disease has been studied for a long time. Thus, the vertebrate hosts and the arthropod vectors are among the unknowns confronting the epidemiologist who seeks to explain the epizootic and epidemic waves of the infection in Central America.

Vertebrate hosts

The high mortality among monkeys is one of the characteristics of the Trinidad and Central American epidemics which contrasts sharply with those of South American outbreaks. In Trinidad and Central America, the progress of the epidemic front could be followed by observation of the deaths among the simian populations, which is impossible in South America. The reason for this lies in the differences in the monkey populations in the two areas.

In South America, particularly in central and southern Brazil, the common monkey is the *Cebus* monkey, howler and spider monkeys being very rare. The *Cebus* monkey, even though it harbours the virus, does not die of the infection. In Central America, on the other hand, *Alouatta* (howler) and *Ateles* (spider) monkeys are much the most abundant species of monkey. They are very susceptible to the infection and die of it in large numbers. In Nicaragua, for example, the passage of the recent epidemic seems practically to have exterminated the monkeys: inhabitants and travellers no longer hear the cry of the howlers which used to be so familiar.

This difference in hosts may have epidemiological repercussions. Where the monkeys have been largely destroyed, it takes years, and even decades, to produce a fresh receptive population; but, since the *Cebus* does not succumb, this monkey is able in a few years to provide a new population capable of transmitting a fresh wave of infection.

[2] According to surveys made during late 1955 in the north of Honduras and in Guatemala, the wave of infection seems to have died out completely.

Thus, in Brazil, the inter-epidemic periods are relatively short as compared with those in Central America, where the last epizootic outbreak among the monkeys appears to have been 25 to 30 years ago. It is suspected that this long interval between epidemics is correlated with the fact that the predominant species is practically wiped out by each epizootic wave of yellow fever.

Thus far only the differences observed among the various genera and species of primates have been mentioned. But another possibility exists: that other families of mammals act as the jungle reservoir of the yellow fever virus. For, as one moves up Central America into Mexico, monkeys become fewer and then disappear, their distribution being roughly coincident with tropical rain-forests. Other mammals, such as marsupials and rodents, may possibly act as reservoirs. In fact, in Colombia marsupials have been experimentally infected by mosquito bites, and the mosquitos feeding on the marsupials have subsequently transmitted the infection to monkeys. In the same country, hundreds of proven fatal cases of yellow fever have occurred in places where monkeys are scarce or absent. It is probable that other mammals have an important role. Marsupials must be considered; they are abundant and prolific and are thus able to ensure the rapid replacement of individuals which become immune by others which are receptive to infection. The study of marsupials—the same species of which are widely distributed in South America as well as in Central America—should be one of the priority subjects in research on the epidemiology of yellow fever in Latin America.

Vectors

In Panama, Costa Rica, and Nicaragua, transmission of yellow fever appears to be related to the presence of the known South American vector *Haemagogus spegazzinii falco*, which is a characteristic inhabitant of the tropical rain-forest. In Honduras the situation is not so clear because monkeys dead of yellow fever were found in a region where this species does not appear to exist. *H. spegazzinii falco* does not reach the north side of the Yucatan peninsula, but several other species of *Haemagogus* do occur in Guatemala and Mexico.

The great variety of observations which have been made in Central America, some of them apparently conflicting, emphasizes how little we really know about the epidemiology of jungle yellow fever, and of the ecology of the jungle hosts and vectors of the virus. A given species—or at least what we think of as a given species—may behave quite differently in two different places, or even at different times at the same place. Furthermore, the results of laboratory experiments are not unreservedly comparable with what takes place in natural surroundings. A mosquito which in the laboratory shows itself to be an efficient experimental vector may turn out to be completely unimportant in its natural environment; and, on the other hand, experience has often shown that a species which acts as a vector in nature may give dubious results in the laboratory. Therefore, the interpretation of ecological and epidemiological observations must be very carefully done if erroneous conclusions are to be avoided.

Virus

In the course of research undertaken by the Rockefeller Foundation on arthropod-transmitted viruses, a considerable number of these were found to fall into either one of two groups according to their affinities as shown by the haemagglutination-inhibition test. Group A includes the three types of equine encephalomyelitis virus, the Semliki Forest virus, and the Sindbis virus. Group B comprises yellow fever, dengue, St. Louis

encephalitis, Ilheus, Japanese B encephalitis, West Nile, Uganda S, Ntaya, Zika, and Russian spring-summer encephalitis.

The viruses in each group are immunologically related to each other, those in group B more so than those in group A. An immune serum prepared against any one of these viruses will, to a greater or lesser degree, inhibit agglutination by an antigen prepared from any other member of the same group, but not by an antigen prepared from the other group. The complement-fixation test and the mouse protection test give confirmatory results. By means of the latter, definite evidence has been obtained that yellow fever virus is related to Uganda S, West Nile, dengue, and Japanese B.

Apart from their immunological characteristics, these viruses have many properties in common: they are all (except Ntaya) of approximately the same size; with all of them, infection of man is an accidental event in the course of a virus cycle in nature; and the complete epidemiological cycle is not yet known for any of them. Monkeys are known to be involved in the cycle of yellow fever and possibly in that of dengue. Birds have been shown to play a part in the West Nile cycle. The mechanism by which the virus is maintained during the season when mosquitos are scarce or absent is known only for Russian spring-summer encephalitis, the virus of which is maintained in ticks.

It can thus be seen that yellow fever virus is only one of a large group of closely related agents, all of which probably evolved from a common ancestral type. Although *Aëdes aegypti* may experimentally transmit other viruses of this group, its role in nature appears to be limited at present to transmission of dengue and of yellow fever.

Such immunological overlaps between viruses may be the cause of cross-immunity phenomena which must be taken into account when considering the susceptibility of certain populations. The possibility cannot be excluded that mass natural immunization against one of these diseases (for example, West Nile in Egypt, or dengue) may produce resistance to another disease such as yellow fever.

* * *

The few points which have been singled out for brief consideration in this article, from among the subjects discussed at the PASB yellow fever conference, emphasize the continuing need for research in the epidemiology of jungle yellow fever on an international scale. Such research should include a study of the fundamental biological facts as they are related to the transmission of yellow fever, of the taxonomy and ecology of the arthropod vectors and mammalian hosts at a variety of places where the disease occurs in endemic and epidemic forms. This all adds up to a study of the natural history of jungle yellow fever.

Two other important matters were dealt with at the conference: the eradication of *Aedes aëgypti*; and international measures for protection against yellow fever.

YELLOW FEVER VACCINATION

About twenty years ago, when vaccination against yellow fever was first applied, no one could have foreseen the enormous advantages which would accrue to countries where the disease was endemic and the security which vaccination would give to populations exposed to risk of infection.

Yellow fever vaccination was made one of the international measures of protection by the International Sanitary Convention for Aerial Navigation of 1944, amending the Convention of 1933. According to the amended Convention, " A valid anti-yellow-fever inoculation certificate is one certifying that the bearer has been inoculated against yellow fever, with a vaccine and by a method approved by UNRRA. . . ." These provisions placed yellow fever vaccine under international control. They did away with quarantine measures; and travellers were no longer exposed to the arbitrary decisions of health authorities, since only one type of vaccination certificate was recognized as valid.

The International Sanitary Regulations, which were adopted in 1951 by the Fourth World Health Assembly and which replaced the conventions in force up to that time, contain the following provisions relating to yellow fever:

> . . . Vaccination against yellow fever shall be required of any person leaving an infected local area on an international voyage and proceeding to a yellow-fever receptive area. . . .
>
> A person in possession of a valid certificate of vaccination against yellow fever shall not be treated as a suspect, even if he has come from an infected local area.

The principle of approval of the vaccine figuring in the 1944 Convention was retained; and, at present, yellow fever vaccination certifications are issued under the authority of WHO. The Organization has the task of designating laboratories approved for the preparation and testing of yellow fever vaccines and has thus assumed a considerable responsibility. Continually expanding research and ever-increasing experience acquired during vaccination campaigns raise problems which must be taken into account in international provisions for protection against yellow fever, and the Organization must keep abreast of such research and experience.

These and other considerations are reflected in a monograph on yellow fever vaccination which WHO has recently published [1] and in which the main aspects of the subject are dealt with by eminent specialists who have taken an active part in research in this field.

Dr K. C. Smithburn, of the Rockefeller Foundation, describes, in the first chapter, the basic principles of yellow fever immunization and the role of passive and active immunity, as well as that of immunological tests in the diagnosis of the disease and identification of the virus. Subsequent chapters, by different authors, deal with the various vaccines and the duration of the immunity which they confer, mass vaccination, post-vaccination accidents, and the international regulations concerning yellow fever.

VACCINES AND VACCINATION TECHNIQUES

Dakar vaccine

The first vaccine against yellow fever consisted of a measured quantity of neurotropic virus neutralized by a corresponding

[1] World Health Organization (1956) *Yellow fever vaccination*, Geneva (*World Health Organization : Monograph Series*, No. 30)

amount of specific serum. This strain of virus had been transmitted to monkeys by the bites of *Aëdes aegypti* fed on a patient in Senegal. In 1928, the virulent organs of one of the monkeys infected in this way were transported in a frozen state to European and American laboratories, where the virus was known henceforward under the name of " French strain ". After a certain number of passages on mouse-brain tissue, this virus became modified in such a way that it no longer brought about the death of monkeys inoculated subcutaneously, but caused mild illness followed by lasting immunity. These properties made it possible to consider using the virus as a vaccine.

In 1931 immunization tests on man were initiated using the French strain, then at its 105-176th mouse passage, with the addition of specific serum intended to neutralize the pathogenic action of the virus. Later, the addition of serum was dropped.

From 1934 on, mass vaccination was carried out in the French territories in Africa south of the Sahara. In 1939, subcutaneous inoculation was replaced by the scarification method, and since 1941 this form of vaccination has been compulsory in all the territories of French West and Equatorial Africa.

For eight years the vaccine produced by the Institut Pasteur of French West Africa, at Dakar, has been a virus at its 258-260th passage through mouse brains, stored in ampoules in the form of dried cerebral tissue of white mice (Fig. 1). At the time of vaccination, the vaccine is suspended in a solution of gum arabic and inoculated by scarification on the upper arm. UNRRA, and later WHO, recognized the validity of the Dakar Institut Pasteur method of vaccination. Between 1939 and March 1954, the Institut produced more than 84 million doses of vaccine. Dr C. Durieux, former director of the Institut, describes in two articles the technique for the preparation and storage of the vaccine and its application.

17D vaccine

From 1931 on, an attempt was made to modify the yellow fever virus by other methods which would reduce not only its viscerotropism, but also its neurotropism, or which at least would not augment it. The tissue culture of a pantropic strain coming from an African of the Gold Coast (the Asibi strain) produced a variant, 17D, which showed attenuated neurotropism for the mouse and for the monkey as well as attenuated viscerotropism for the latter. When inoculated intracerebrally, this strain no longer brought about fatal encephalitis in the monkey but protected it against highly virulent pantropic strains. The strain could be readily cultivated on chick embryo, had the advantage of not introducing into the human organism latent viruses from the mouse, and appeared suitable for use in man with a minimum of risk.

17D vaccine has been used since 1937, and is at present employed in most parts of the world. Dr H. A. Penna, in charge of the Yellow Fever Laboratory of the Instituto Oswaldo Cruz, Rio de Janeiro, describes in detail the production of the vaccine in this institute, which houses one of the principal laboratories preparing yellow fever vaccine. Every week this laboratory receives 2000 eggs for the culture of the virus, corresponding to a monthly output of 1.5 million doses of vaccine. New laboratories which are under construction will make it possible to double the output. The vaccine is put into ampoules in which the embryo suspension is shell-frozen and dried.

In a second article, the same author considers subcutaneous vaccination techniques with this vaccine, particularly as practised in Brazil.

17D and scarification

Since the scarification method had given excellent results with Dakar vaccine, an

FIG. 1. STORAGE OF YELLOW-FEVER VIRUS IN FROZEN AND DRIED MOUSE BRAINS

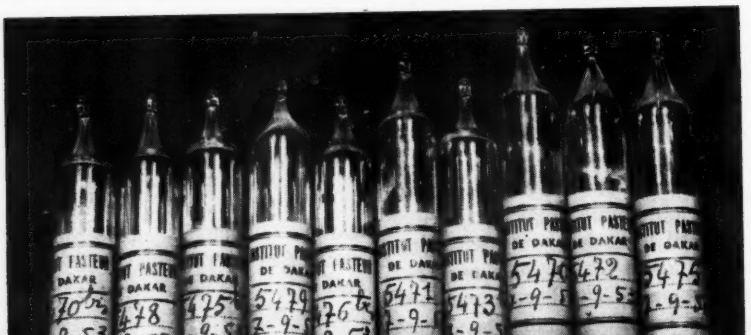
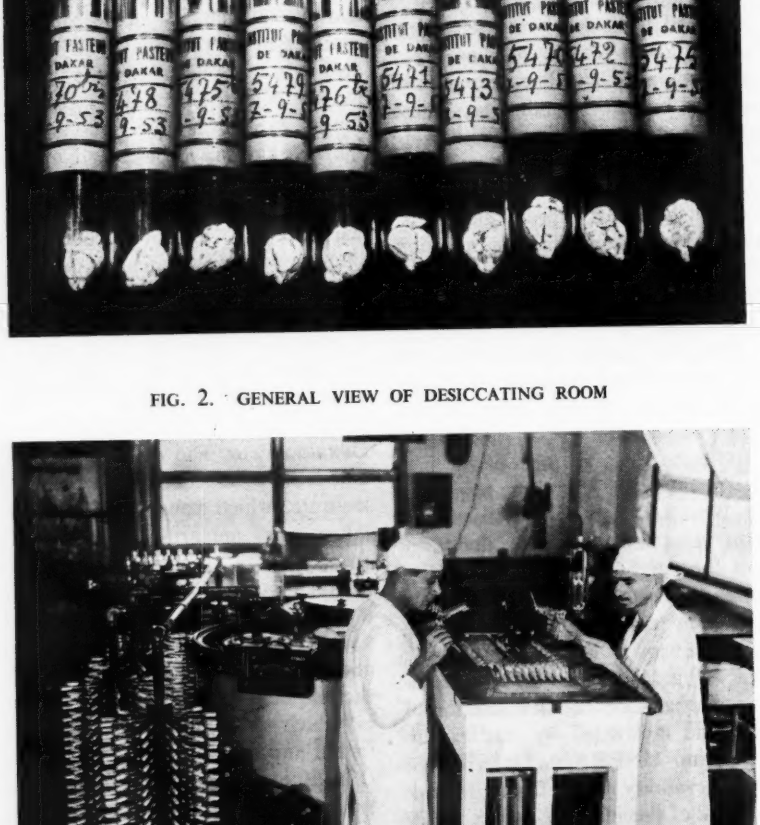


FIG. 2. GENERAL VIEW OF DESICCATING ROOM



One lot of vaccine is in the final stage of desiccation. Another lot is being frozen in ampoules and being placed in the chilled desiccator (hidden by the deep-freeze).

attempt was made to apply it to vaccination with 17D.

Dr G. W. A. Dick, of Queen's University, Belfast, discusses the advantages of this method. When administered by scarification, 17D vaccine is an excellent antigen, even in high dilutions. It is probably even more active when so administered. This method is more economical, since all the embryo suspension—coming from the decapitated embryo—may be used, whereas a third is discarded in the preparation of subcutaneous vaccine. Less strict bacterial sterility is acceptable, which reduces the cost. It would seem that, to give the same protection, smaller amounts of antigen are required when administered by scarification than by the subcutaneous route. The author suggests that mass vaccination with 100 mouse intracerebral LD_{50} of virus should be investigated. If this dose were found to be adequate, a 5-ml ampoule would be sufficient to vaccinate 1000 persons, thus reducing the cost of vaccination to one-tenth of the present figure. The author also discusses the advisability of combined smallpox-yellow fever vaccination.

DURATION OF IMMUNITY

The duration of the immunity conferred by yellow fever vaccine and the moment when the antibodies appear in the blood have been the subject of experimental research in man and animals since 1931. G. Courtois, Director of the Stanleyville Medical Laboratory, and C. Durieux & R. Koerber, of the Institut Pasteur at Dakar, arrive at similar conclusions for 17D vaccine and for Dakar vaccine, respectively. Originally put at 4, 6, or 9 years, the duration of immunity is now estimated to be at least 12 years, in the light of antibody titrations carried out in 1953 on subjects vaccinated in 1941. It is possible, as Mahaffy has suggested, that it will eventually be found that immunity is lifelong.

At present the vaccination certificate is valid for six years. From the tenth day following vaccination the antibodies present in the serum ensure appreciable protection. This period is a little shorter in the rhesus monkey. However, in the monkey, as in man, a certain resistance to infection appears before the antibodies are detectable in the serum. The nature of this protection is still unknown.

MASS VACCINATION

Ever since standard methods for the preparation of large quantities of vaccine have been available, mass vaccinations have been carried out in Africa and in South America—large-scale vaccination commenced in 1934 in the French territories south of the Sahara, and in 1937 in Brazil. Dr C. Durieux, in an article on this subject, states that the number of vaccinations in the French territories exceeded 56 million at the end of 1953, which meant that each inhabitant had been vaccinated twice. After 1943, the prevalence of the disease decreased, although at that time only half the population had been vaccinated. During the past 20 years, the number of cases of yellow fever has continually decreased, dropping from 134 in the period 1934-48 to 5 in the period 1949-53.

In South America nearly 22 million persons were vaccinated with 17D vaccine between 1937 and 1954, according to Dr C. de Souza Manso in an article on mass vaccination in Brazil. This author also describes the preparation of vaccine for use in the field and discusses the influence of vaccination on the spread of jungle yellow fever.

POST-VACCINATION ACCIDENTS

The question of post-vaccination accidents has given rise to much controversy. Dr G. Stuart, former Chief of the WHO Quarantine Service, discusses in detail the reactions caused during the past 15-20 years by the various types of vaccine, with or without the

addition of serum. Some reactions do not affect the central nervous system (e.g., allergic reactions, fever, serum hepatitis); others, occurring 10-20 days after vaccination, include a meningo-encephalitis syndrome with motor, sensory, mental, or lethargic manifestations.

The Dakar vaccine, in particular, has given rise to accidents, sometimes fatal, in the French African territories and in Nigeria, Costa Rica, and Nicaragua. Encephalitic accidents have also occurred with 17D vaccine, and mild sporadic cases have been reported in very young children in the years 1953-55.

Several explanations have been offered for these accidents. It has been suggested that the cause of the accidents with the Dakar vaccine is the increased neurotropism of virus cultivated on the mouse brain or the activation of a virus latent in man. However, a fall in the titre of the vaccine because of faulty preservation of the ampoules in the field would seem more likely to be responsible.

INTERNATIONAL REGULATIONS AND RELATED PROBLEMS

Although its basic principles have been established, vaccination against yellow fever continues to be the subject of research and technical improvement. The responsibility assumed by WHO in approving vaccines intended for international use makes it necessary for the Organization to keep in close touch with such work, as has been previously suggested.

In an article on the role of WHO, Dr P. H. Bonnel, of the Division of Epidemiological and Health Statistical Services, after having outlined the history of the conventions and international regulations relating to yellow fever vaccination, enumerates the requirements which vaccination certificates must fulfil in order to be accepted in international traffic, and lists the problems which WHO faces in connexion with the approval and control of yellow fever vaccines.

ENDEMIC TREPONEMATOSES CONTROL *

International Yaws Conference in Africa

In the rural areas of the tropical belt of the world live about 400 million people of whom approximately half are exposed to the risk of infection with yaws and other endemic treponematoses. Mass treatment campaigns, based on the use of single injections of long-acting penicillin, have, in recent years, given impressive results in many of these areas. These campaigns have been carried out, under the supervision of professionally qualified personnel, by simply trained auxiliaries who can subsequently be employed in other field activities and in local health services. In some countries such campaigns have become an important factor in the development of comprehensive rural health services.

In November 1955, WHO convened a second international conference on yaws control to review the present situation and to provide technical guidance to health administrations in their future plans for treponematoses-control programmes. This conference, which was attended by 53 participants from 30 countries, was held in Enugu, Eastern Nigeria. It was fitting that it should have taken place in Africa, for about half of the estimated 50 million cases of yaws which exist in the world are found in that continent.

* This account was prepared by Dr R. R. Willcox, WHO Treponematoses Consultant.

The Eastern Region of Nigeria was chosen as the site of the conference because an active yaws-control campaign is in progress there, which made it possible for participants to observe field activities.

The conference considered that, with the public health techniques now available, the endemic treponematoses could be eliminated as health problems in the less-developed areas. Many health administrations had already launched treponematosis-control campaigns in the Western Pacific Region, in South-East Asia, and in the Americas, and projects were being developed in Africa. Over 50 million persons had been examined and 15 million treated in such campaigns throughout the world with assistance from WHO and UNICEF. However, further work was needed in these international campaigns.

The conference proposed that a co-ordinated offensive against the endemic treponematoses, particularly yaws, be undertaken in Africa with assistance from WHO and UNICEF over the next few years.

At the same time, participants at the conference emphasized the need for continuing studies on the fundamental problems relating to the treponeme, the host, and the environment, and for assembling all available data on the nature, extent, epidemiology, and biology of the endemic treponematoses. Much new information on the latter subject was forthcoming from the International Treponematosis Laboratory Center at Johns Hopkins University in Baltimore, Md., USA. Information on the prevalence of the various treponematoses—sporadic venereal syphilis, endemic syphilis, yaws, and pinta—in different parts of the world was also needed. The pooled experience of those present at the conference gave evidence, for example, of a greater prevalence of endemic syphilis in Africa than had been realized.

The conference was concerned particularly with the technical aspects of mass campaigns to control the endemic treponematoses.

PLANNING AND CONDUCT OF CONTROL CAMPAIGNS

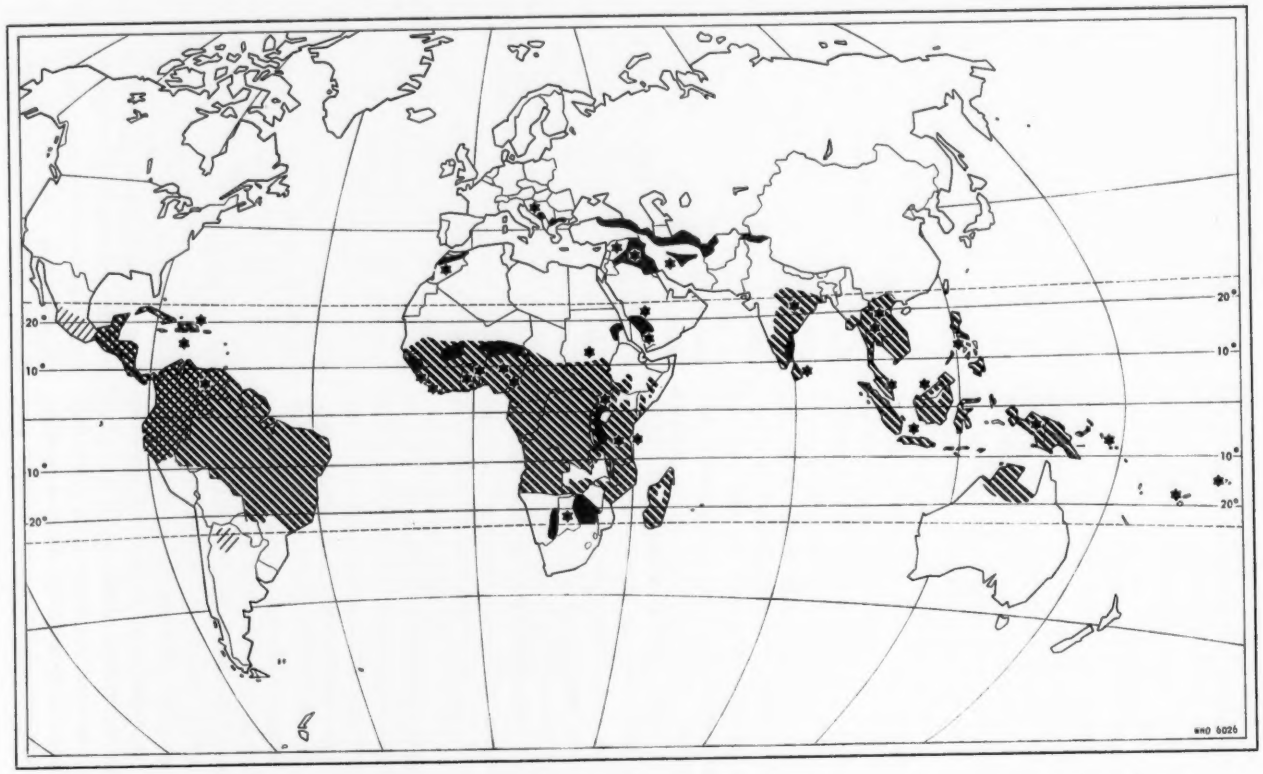
In planning a yaws-control campaign all the stages of such a campaign should be taken into account—not just the period of mass treatment, but also the consolidation phase and the eventual integration of yaws-control activities into the permanent health organization of the country. If all stages are not provided for, there is danger that, although yaws-control teams may succeed in eliminating the disease in a particular area, absence of facilities to maintain the control will lead to ultimate failure.

Conference participants expressed the fear that " local conditions " might sometimes be used as a convenient excuse for inadequate performance of control activities. These conditions should influence only the method of approach, the basic principles of endemic treponematoses control remaining unchanged regardless of place.

General approach

In principle, multipurpose activities (i.e., health activities in addition to those directed against the endemic treponematoses) should be the ultimate goal of a programme to control endemic treponematoses. At the stage of mass treatment, however, the main effort should be directed against yaws—or the endemic treponematosis in question—although some secondary activities, such as simple out-patient treatment of other illnesses, are unavoidable and, indeed, desirable. In many areas there are diseases more serious than yaws (e.g., sleeping sickness and malaria), and under such circumstances it may be desirable to concentrate first on the more serious disease, giving yaws priority as soon as the control of the other disease has been achieved. Other health activities, such as leprosy case-finding, smallpox and yellow fever immunization, and others, can sometimes profitably be combined with a yaws-control programme. For example, during

FIG. 1. GEOGRAPHICAL DISTRIBUTION OF THE NON-VENEREAL TREPONEMATOSES AND INTERNATIONALLY ASSISTED CONTROL PROJECTS



mass screening for yaws in the Nsukka Division of Eastern Nigeria, with a population of approximately 350 000, about 1700 persons suffering from leprosy were discovered and directed to appropriate centres for treatment. However, such activities should not be permitted to weaken or retard the rapid expansion of the endemic-treponematoses-control campaign.

Community co-operation

The conference participants stressed the necessity of ensuring that all levels of the community fully understand the objectives of the treponematosis-control campaign. It is particularly important that the co-operation of local leaders and headmen be secured, as an aid in obtaining the necessary coverage of the population. The spectacular results of treatment of yaws with penicillin are most effective in gaining the co-operation of the people. However, the effect is maximal when there is much yaws; and interest is likely to wane during the period of resurveys, when only a few cases are found.

FIG. 2. MASS CAMPAIGNS AGAINST YAWS IN AFRICA—I

It is largely owing to the dramatic results obtained with appropriate control measures in mass campaigns that the populations covered co-operate fully with the public health personnel. Above : Liberian boy disfigured by yaws lesions, and a fortnight after treatment.

Population coverage

It was accepted by all the conference participants that 100% coverage of the population should be the aim in the initial treatment survey, and a coverage of less than 90% was considered inadequate. Comprehensive data from Indonesia supported this view.

There are several methods by which full coverage can be achieved. One is by house-to-house visiting, making a nominal roll. Another is by enlisting the aid of the local chief and village headman in assembling the entire population at a convenient place and checking the total attendance of the particular community with the most recent census figures, if such figures are available.

Penicillin treatment

Single injections of a long-acting penicillin preparation continue to give impressive results in the treatment of yaws, and have also been successfully used in the mass treatment of endemic syphilis.

To date there are no signs of penicillin resistance in the treponeme. Side-reactions, which have been reported in small numbers in some countries, are so far not of public health importance in mass campaigns. In fact, in the rural areas where penicillin is being used in mass treatment of the treponematoses, this drug has not been employed previously; and sensitization reactions are rare. The conference participants felt that now was the time to take advantage of this highly favourable situation.

The usual adult dose is a minimum of 1.2 mega units of a PAM preparation meeting WHO specifications,[2] with proportionately lower doses for children. This dose represents a calculated risk—a compromise between maximum efficacy and practical economy—aimed, as a public health measure, at curing the vast majority of infectious cases and at stopping the transmission that maintains the reservoir of infection. It is successful in curing a high proportion of latent cases and late cases as well.

It was noted at the conference that three-fourths of infectious yaws cases are in children below 15 years of age, and that in these cases progressively lesser amounts of penicillin have been given, according to age. However, reports of a carefully controlled series of dark-field positive cases of early yaws in Haiti revealed highly satisfactory results with single injections of 0.6 mega units of PAM; and the conference participants thought it advisable to recommend this dosage for all children under 15 years of age. In view of the decrease in the price of penicillin in recent years, the extra cost involved, when the whole cost of a campaign is taken into consideration, is no longer as significant a budgetary factor as formerly.

There was general agreement that half of the dose of penicillin administered to clinical cases should be given to latent cases and to contacts.

The results obtained with the newer benzathine penicillins in the treatment of yaws were reviewed at the conference. Dose for dose, benzathine penicillin gives a more-prolonged penicillinaemia than PAM, and it has been reported to be more efficient in the treatment of hyperkeratosis. However, unit for unit it is more expensive; its durability in the tropics in the pre-suspended form is less; and many observers have reported local pain with its use. More information is required before replacing PAM by benzathine penicillin can be considered in the treatment of yaws.

Treatment policies

The total reservoir of yaws consists of clinical cases, latent cases, and those in the incubation period. Clinical cases may be early infectious cases, or late cases. The

[2] See *Wld Hlth Org. techn. Rep. Ser.*, 1953, 63, 22, 55.

FIG. 3. MASS CAMPAIGNS AGAINST YAWS IN AFRICA—II

Orderly organization is an important element in the success of a mass campaign. Above : A line of Nigerians awaiting treatment. The chief, who maintains order, may be seen walking in the foreground.

number of infectious cases in relation to the latent cases is usually small; and, since primary lesions are generally few, the number of cases in the incubation period at any one time is also small. The greatest problem arises from early latent cases, which may give rise to infectious relapses for some years. Late latent cases, which contribute much less to the spread of the disease, may give rise to incapacitating and mutilating late lesions. The latent cases cannot be accurately determined without the use of serological screening, which is not usually feasible in a mass campaign on account of the cost and the loss of speed involved. Finally, there are the contacts to be dealt with.

In view of these considerations, it is evident that treating clinical cases alone is unlikely to eliminate yaws, as cases in the incubation period and early latent cases are missed. Reports of experience in the Philippines and in Indonesia have confirmed this. Even with repeated resurveys at short intervals, the reduction in prevalence is uneconomically slow. Some form of mass treatment which reaches non-clinical cases that are liable to relapse with infectious lesions must therefore be devised.

To date, three policies of mass treatment have been tried:

(1) Total mass treatment, arbitrarily recommended when the prevalence of active cases exceeds 10% of the population. Under these circumstances, the entire population is treated, a full dose of penicillin being given

FIG. 4. MASS CAMPAIGNS AGAINST YAWS IN AFRICA—III

To use time to the best advantage, it is essential that the examiners be supplied with a regular flow of patients. Above : A group of Nigerian women waiting their turn to be examined.

to clinical cases and half the dose to latent cases and to contacts.

(2) Juvenile mass treatment, recommended when the prevalence of active yaws is within 5-10%, and consisting of the treatment of all children under the age of puberty in a given area and of infectious cases and their contacts regardless of age. This method was devised to cover the largest number of those likely to develop infectious lesions with the greatest economy in penicillin.

(3) Selective mass treatment, in which only active cases and household and other obvious contacts are treated. This is recommended when the prevalence of active yaws is less than 5%.

The general opinion at the conference was that total mass treatment might well be employed even when lower prevalences than those indicated above are found, and that juvenile mass treatment was preferable to selective mass treatment. Although at first sight total mass treatment seems extravagant

of penicillin, it is likely to be more economical in the long run because the sorting-out of household contacts is avoided, the speed of the campaign is increased, and resurveys are needed less frequently.

Use of serological tests

It was agreed that the use of serological testing in a total mass campaign, in which all persons are treated, is unnecessary and wasteful of time, equipment, and personnel. In hyperendemic areas, the prevalence of active cases is a sufficiently sensitive index, for all practical purposes. In areas of low prevalence, in which active cases and household and other contacts only are usually treated, serological screening is used to identify latent cases.

Serological testing is desirable in preliminary pilot studies made in the planning stage to determine the prevalence of treponematoses and, therefore, the nature of the campaign to be undertaken. It is also useful in appraising the results of the mass campaign. For the latter purpose, sample surveys may be used; and means of carrying out such surveys were discussed at the WHO conference. Evidence was presented to suggest that use of cardiolipin antigens in conventional serological tests in Africa reduces the percentage of biological false positive results.

Conference participants felt that the latest advances in the serodiagnosis of the treponematoses—such as the treponemal immobilization test, the treponemal agglutination test, and the treponemal complement-fixation test—were unlikely to be of value in a mass campaign. They should be used, however, on a research basis, to check the results obtained by the teams with conventional tests, to determine the prevalence of biological false positive results, and to provide data about immunity and other problems relative to the endemic treponematoses.

Resurveys

Resurveys are used not only to ensure the success of the initial treatment survey, but also to obtain data by which the success or failure of the campaign as a whole may be assessed. During resurveys cases missed in the initial survey which have become active in the meantime, relapsing cases, and cases which have moved into the area—plus the contacts of all of these groups—are found and treated. Provided that adequate coverage has been obtained in the initial treatment survey, the greatest danger is from immigrants into the treated area. This emphasizes the need for simultaneous campaigns in adjacent areas (see below).

The first resurvey should be undertaken between 6 months and a year after the initial treatment survey, depending on the degree of coverage at the beginning. Subsequent resurveys should take place approximately every 12 months, and should be continued until the local rural health services are sufficiently developed to take care of the few active cases that are likely to occur.

Appraisal of results

The conference participants considered post-treatment evaluation studies from a number of areas. In Haiti, for example, sample surveys, made approximately two years after treatment, have shown that the prevalence of yaws has been reduced to 50 per 10 000 of the population for all cases of yaws, and 15 per 10 000 for infectious cases. And in the Nsukka Division of Eastern Nigeria, where before treatment the prevalence of active yaws was 1380 per 10 000 of the population (infectious cases: 300 per 10 000), the rate had decreased, in the various subdivisions, to 0-30 per 10 000 of infectious cases one year after treatment.

Such post-treatment evaluations have provided evidence that the prevalence of yaws can be rapidly and effectively reduced by

single injections of repository penicillin to a level at which it no longer represents an immediate public-health problem.

GEOGRAPHICAL EXPANSION OF A MASS CAMPAIGN

The conference was concerned with the risk of reintroduction of infection from outside a treated area. The endemic treponematoses recognize no geographical or tribal frontiers, and movement of people to and fro across such frontiers is frequent.

The most effective way of preventing reintroduction of infection is through uniform expansion from the centre of operations and co-ordination of the simultaneous development of similar campaigns in adjoining territories. It is logical, therefore, that health administrations of countries in which yaws and endemic syphilis are found should be urged to co-ordinate their activities in an effective manner. This is particularly important in Africa, which has many interlocking political frontiers, totally unrelated to geographical barriers, which might limit the spread of disease. Every day countless

FIG. 5. MASS CAMPAIGNS AGAINST YAWS IN AFRICA—IV

Efficient organization of the various stages of the procedure is vital to the proper running of a mass campaign. Above : The syringe table. The caps are removed from 10-ml vials of penicillin, the syringe is filled and the needle attached. After each injection, the needle is discarded and a sterile needle used for the next injection.

thousands cross these frontiers; and migrations, for religious or economic reasons, are constantly taking place, on a continental or subcontinental scale.

In connexion with the Africa-wide, co-ordinated offensive against the endemic treponematoses mentioned earlier, it was proposed that a conference of health administrators be convened as soon as possible to prepare this vast campaign.

VENEREAL SYPHILIS AND OTHER VENEREAL DISEASES

Reliable figures concerning the prevalence of the different venereal diseases in Africa are scanty. Such diseases are concentrated largely in the towns, although in some areas gonorrhoea has spread widely into rural districts as well.

It was observed at the conference that the traditional methods of control, based on contact-tracing of individual cases, are unlikely to succeed in Africa at present. The facilities for such work are not yet sufficiently developed.

Of some concern is the possibility that venereal syphilis might be reintroduced into areas cleared by mass campaigns and find the environment still favourable for endemic spread. Conference participants therefore considered that, when campaigns against the endemic treponematoses are being planned, provision should be made for co-ordinating a programme to deal with venereal syphilis in the towns.

POST-CAMPAIGN ACTIVITIES

In the less-developed countries, an essential factor in the development of health services is the establishment of local rural health services, which are, however, largely dependent for their success on the goodwill of the people they serve. The conspicuous results of penicillin treatment in the endemic treponematoses can be immediately understood by the general population and help to give them a broader understanding of the importance of good health, thus providing a basis for popular participation in future health work. It is therefore appropriate to time the carrying-out of plans for rural health centres to coincide with campaigns to control the endemic treponematoses; it is preferable that these centres should be functioning before the campaign is over in a given area, so that they may assist in the control and, ultimately, the eradication of the disease and help to reduce the number of resurveys. In this way, too, staff from the control campaign can be integrated into the permanent health structure of the country.

Post-campaign activities should also be co-ordinated with those of other services —agricultural, veterinary, educational, and voluntary social and political organizations. Two particularly important developments are the improvement of communications and the improvement of sanitation, including the provision of adequate water supplies to villages.

CONCLUSIONS

In the past, efforts to control endemic treponematoses frequently failed because of inadequately organized and co-ordinated campaigns, incomplete coverage of the population, emphasis on the clinical rather than the epidemiological aspects of the disease, the unsuitability of metal chemotherapy for mass campaign work, and unchanged environmental conditions which favour the spread of disease. Today, most of these factors have been eliminated. Penicillin has proved itself an effective weapon for mass control work, the treponeme has shown no signs of resistance, and penicillin side-

reactions are not, as yet, of public health importance. Mass campaigns are now relatively inexpensive and involve little or no capital outlay. The total cost of campaigns in South-East Asia—including penicillin, transport, local staff, administration, and other expenses—is now US $60 000 to $80 000 (£20 000 to £30 000) per million persons examined. In a word, eradication of the endemic treponematoses is within reach. Indeed, it is of great economical and physical importance, for in yaws, for instance, the onset of infection occurs in children, resulting in incapacity for work among the young and in mutilation and invalidism in an appreciable percentage in the existing and future labour force. Thus, in several campaigns more than 50% of the yaws patients treated had disabling palmar and plantar lesions while some 10% had late disfiguring or crippling lesions.

By the rapid and obvious results of penicillin treatment an understanding of health and a co-operative attitude among the population are created which are favourable to the development of further health activities and which provide an opportunity to strengthen and co-ordinate rural health services in the wake of the control campaign and to raise the standard of living of the people.

In many countries and regions of the world, co-ordinated campaigns are already actively under way, but in Africa, which contains the largest continental reservoir of endemic treponematoses, estimated at 25 million cases of yaws alone, they are only beginning. The conference participants therefore recommended that an offensive to control endemic treponematosis be undertaken in Africa on a continental scale under the general co-ordination of WHO.

LABORATORY ASPECTS OF THE TAIWAN SYPHILIS-CONTROL PROGRAMME *

A syphilis-control project, which included the establishment of an island-wide serological laboratory service, was started in Taiwan in the autumn of 1953 by the Government and WHO, with UNICEF assistance. Though certain serological tests for syphilis had been carried out in a few provinces of the island before the advent of the control programme, no serological service had been made generally available to the public. The tests were, moreover, of questionable reactivity, since there had been no attempt to standardize them.

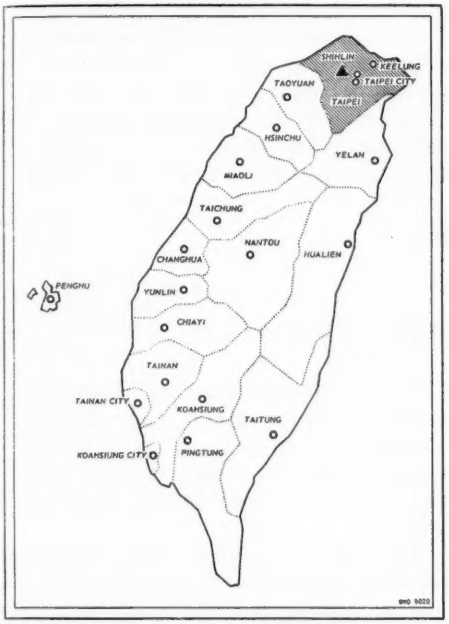
The organization of laboratory services was part of the general syphilis-control programme. A demonstration area was set up to serve as a training centre for all personnel. This area comprised all of Taipei *hsien*, including the port city of Keelung. A syphilis-control centre was located at the Taipei Provincial Health Centre, and a "model project" was established at the Taipei Provincial Hospital, both in Taipei City. A serological reference laboratory to serve the laboratories in the *hsien*, or provinces, was established at the Taiwan Serum Vaccine Institute, Shinlin, about two miles outside the city of Taipei.

In all, 21 laboratories were organized in 10 provinces (see Fig. 1): four in the demonstration area, counting the reference laboratory, one in each of the *hsien*, and one in each of the major cities.

Training of clinical and other personnel for the control programme was undertaken in

* Based on reports by Dr Ping-Nan Wang, Chief, Reference Laboratory, Taiwan Venereal Disease Control Programme, and Mr W. H. Gaub, WHO Laboratory Adviser for this project, and on reports of Dr O. Idsoe, WHO Chief Medical Adviser for the project

FIG. 1. DISTRIBUTION OF TAIWAN LABORATORIES, 1953-55



WHO demonstration area
▲ *Reference laboratory*
o *Serological laboratory*

the syphilis-control centre and in the " model project ". Training of laboratory personnel was done at the reference laboratory. Altogether, over six hundred physicians, nurses, and auxiliary personnel were trained over a period of two years; and twenty-eight technicians were given eight weeks of intensive instruction not only in the performance of routine serological procedures, but also in the operation of a serological service. The reference laboratory also participated actively in the training of medical and nursing personnel.

The new laboratory service included standardization of equipment, techniques, and antigens and reagents, and uniform reporting and record-keeping. The procedures routinely taught to, and employed by, the technicians were the VDRL slide test, using cardiolipin antigen, and the Kahn test. The qualitative and quantitative VDRL tube test was performed upon spinal fluid specimens.

From the beginning of the project, in the last quarter of 1953, to the last quarter of 1955, 427 452 blood specimens were tested. The data which follow show the gradual increase in the number of operating laboratories and in the volume of work up to the first quarter of 1955.

Period	*Number of laboratories operating*	*Number of blood specimens*	*Reactors (%)*	*Total tests performed*
4th quarter 1953	1	3 193	13.0	4 981
1st quarter 1954	1	1 985	21.4	2 826
2nd quarter 1954	10	19 444	17.3	25 868
3rd quarter 1954	20	35 539	20.9	46 392
4th quarter 1954	21	60 460	17.1	79 190
1st quarter 1955	21	84 697	13.6	106 892
Totals	21	205 318	16.3	266 149

Periodically, all the laboratories were visited by the WHO-appointed venereologist, the laboratory adviser, and the national chief of the reference laboratory to check on the performance of the standardized procedures. In addition, the technicians' test performance was subjected to an annual evaluation. A high level of performance was observed among the laboratories in a survey made in late 1954 and early 1955 in which the minimum standards were: specificity—no less than 99.0%; sensitivity—not over 10% less than that attained by the referee laboratory with the same test and in the same survey. Refresher courses were arranged for technicians who failed in the evaluation survey, and other courses of a similar nature have been planned for interested personnel.

The laboratory participated in mass surveys, numbering 104; assisted in establishing a " field laboratory " in conjunction with a survey conducted in an isolated coal-mining village near Keelung; undertook a comparative study of the VDRL slide, Kline standard slide, Kahn standard, and Meinicke slide (Kvittingen technique) tests; and co-operated with the International Treponematosis Laboratory Center in Baltimore, Md., USA, in the study of the new *Treponema pallidum* agglutination test.

This project in Taiwan has demonstrated that standardization of laboratory services results in economy of field and clinic operation and greatly facilitates dealing with problems of supervision and co-ordination in a national syphilis-control programme.

MORTALITY FROM DIABETES MELLITUS

Sugar diabetes (diabetes mellitus) has always been considered an important cause of morbidity and mortality, not only in itself but more particularly on account of the way in which it aggravates the course of a number of other disorders. There is little available international information on morbidity; but a series of statistical tables with explanatory notes was recently published in the *Epidemiological and Vital Statistics Report*,[1] and some of these tables give information dating back to the beginning of the century.

Diabetes was already included in the Bertillon Nomenclature, which was adopted as the international list in 1893. From the original rubric, the following were later separated: diabetes insipidus (1909), diabetic pigmentary cirrhosis or " bronzed diabetes " (1938), renal glycosuria or " renal diabetes " (1948).

For obvious reasons, these changes had very little effect on the statistical series. The same cannot be said, however, of a number of variable factors—no doubt common to all statistics on mortality by cause, but particularly noticeable in so far as diabetes is concerned. Among these factors are: inexact diagnoses of causes of death; imperfection of death-registration systems; changes in the population structure; and, particularly, variations in the criteria adopted for the determination of cause of death when—as happens more and more frequently—several diseases are mentioned on the death certificate.

In order to overcome this difficulty a number of countries have established rules for the selection of the cause to which death is to be attributed. These rules, however, are not uniform, and in some cases they have been altered on the coming-into-force of a new nomenclature. There are, therefore, considerable divergencies in the statistical series for deaths from diabetes mellitus, not only from one country to another, but also in one and the same country over different periods. The only period to which this perhaps does not apply is that of the last few years, since the application of the provisions of the last revision of the International List (1948); and it will thus be realized that comparison of these series could lead to serious mistakes. The figures in the tables in the *Report* in question cannot be considered as anything more than a basis for more thorough study. Previously no such basis was available.

Below are given some examples of the consequences of the adoption of new rules

[1] *Epidem. Vital Statist. Rep.*, 1935, **8**, 467-512

TABLE I. DISTRIBUTION IN DENMARK, ACCORDING TO TWO METHODS OF CLASSIFICATION, OF UNDERLYING CAUSES OF DEATHS IN CONNEXION WITH WHICH DIABETES MELLITUS IS MENTIONED *

Death attributed to	Danish rules for selection of underlying cause %	New rules for selection of underlying cause %
Diabetes as underlying cause	54	7
Other underlying causes	46	93
including:		
diseases of the circulatory system	22	55
malignant neoplasms	10	10
diseases of the genito-urinary system	3	10
tuberculosis (all forms)	2	2
diseases of the respiratory system	1	5
other causes	8	11

* With respect to 1539 medical certificates of death from January 1949 to 30 June 1951; percentage of certificates mentioning diabetes mellitus.

for the determination of the underlying cause of death.

In *Canada*, the introduction in 1950 of the new International List caused the number of deaths attributed to diabetes mellitus to drop from 2749 in 1949 to 1544 in 1950, giving a drop in specific mortality from 20.5 to 11.3 deaths per 100 000 inhabitants. This is a purely fictitious decrease; for, if the 1949 data had been reclassified on the basis of the new international criteria, only 1508 deaths would have been attributed to diabetes mellitus in that year.

In the *United States of America*, the figures for deaths from this same cause dropped from 38 638 in 1948 to 25 089 in 1949, the year in which the sixth revision of the International List was applied. This is also a fictitious drop from 26.4 to 16.9 deaths per 100 000 inhabitants.

TABLE II. DEATH RATES FROM DIABETES MELLITUS IN CERTAIN COUNTRIES, BY SEX, 1951-53

(Mean annual rate per 100 000 population of each sex)

Country	Males	Females	Total
Union of South Africa [1]			
European population	6.5	13.5	10.0
Canada	9.0	13.1	11.1
United States of America	12.7	19.8	16.3
Ceylon	8.5	4.8	6.8
Israel	2.9	4.1	3.5
Japan	2.4	2.5	2.4
Germany, Federal Republic	7.7	13.1	10.6
Austria	5.8	9.1	7.6
Denmark	4.7	6.8	5.7
Spain	4.7	7.8	6.4
Finland	4.2	7.7	6.0
France	7.9	13.8	10.9
Ireland	6.9	7.8	7.4
Italy	7.5	11.1	9.2
Norway	6.1	8.2	7.2
Netherlands	6.8	15.8	11.3
Portugal	4.4	6.0	5.3
United Kingdom:			
England and Wales	5.3	10.0	7.8
Scotland	6.0	12.9	9.6
Northern Ireland	4.7	7.1	5.9
Sweden	8.4	13.8	11.1
Switzerland	10.1	18.2	14.3
Australia			
Excluding full-blooded aboriginals	8.4	16.7	12.5
New Zealand			
Excluding Maoris	9.1	16.1	12.6

[1] 1950-52

In *Denmark*, the same thing happened in 1951: from 966 deaths (22.6 per 100 000 inhabitants) in 1950, the figure fell to 294 (6.8) for the following year. Before 1951,

TABLE III. INDEX OF INCREASE, FROM THE AGE OF 40-49 YEARS, OF MORTALITY ATTRIBUTED TO DIABETES MELLITUS IN CERTAIN COUNTRIES, 1951-53 (40-49 YEARS = 100)

Country	Males					Females				
	Age-group (years)									
	40-49	50-59	60-69	70-79	80+	40-49	50-59	60-69	70-79	80+
Union of South Africa [1]										
European population	100	265	759	2 292		100	394	1 562	3 217	
Canada	100	337	871	1 888	2 841	100	503	1 703	3 087	3 482
United States of America	100	289	803	1 681	2 363	100	414	1 329	2 377	2 764
Ceylon	100	337	687	1 157	1 667	100	328	572	830	782
Israel	100	850	1 900	5 800		100	500	2 100	4 621	
Japan	100	308	600	808	508	100	252	537	648	419
Germany, Federal Republic [2]	100	331	1 246	2 512	2 735	100	476	1 988	4 396	3 912
Austria [2]	100	217	650	1 357	857	100	521	2 029	4 086	3 764
Denmark	100	258	879	1 758	2 379	100	296	1 113	2 326	1 822
Spain [3]	100	267	733	1 600	1 800	100	367	1 100	2 333	2 200
Finland	100	438	1 175	2 125	969	100	344	1 889	4 017	2 833
France	100	250	792	1 622	1 783	100	452	1 519	3 015	2 637
Ireland	100	167	316	730	1 254	100	333	700	1 464	1 272
Italy	100	400	308	3 308		100	515	2 012	3 642	
Norway	100	176	497	1 206	2 171	100	274	952	2 604	3 687
Netherlands	100	278	1 333	4 372	8 222	100	571	3 053	10 324	18 071
Portugal	100	300	717	1 470	1 227	100	288	828	1 484	1 322
United Kingdom :										
England and Wales	100	225	790	2 270	3 270	100	345	1 465	3 275	3 845
Scotland	100	236	661	1 664	2 982	100	441	1 494	2 822	2 306
Northern Ireland	100	350	913	2 619	1 875	100	200	735	1 429	2 206
Sweden	100	255	726	2 177	2 803	100	414	1 845	4 782	5 418
Switzerland	100	500	1 846	2 912	4 073	100	603	2 207	4 470	4 980
Australia										
Excluding full-blooded aboriginals	100	412	1 408	3 438	4 877	100	574	1 847	4 485	5 462
New Zealand										
Excluding Maoris	100	364	1 428	3 152	5 600	100	585	1 908	5 754	6 892

[1] 1950-52 [2] 1952-53 [3] approximate figures

the deaths of all diabetics (with the exception only of persons also suffering from tuberculosis or cancer or meeting a violent death) were attributed to diabetes mellitus, whereas now the diabetes mortality statistics cover only death from diabetic coma and deaths of persons on whose certificate diabetes appears as the only disease. Table I, an extract of an analysis made by K. Dreyer & A. Hey,[2] illustrates more clearly than any commentary the interruption in the continuity of the statistical series in 1951.

[2] Dreyer, K. & Hey, A. (1954) *Ugeskr. Læg.* 116, 273

In *England and Wales*, on the other hand, the break occurred in 1940. In that year, new rules for the statistical classification of causes of death were applied—rules very similar to the international criteria which were to be adopted after the sixth revision of the International List. In fact, the number of deaths attributed to diabetes mellitus showed a marked decrease between 1939 and 1940—7627 (18.5 per 100 000 inhabitants) in 1939 as against 5346 (13.4) in 1940.

Many more examples could be cited. But those that have been given suffice to show that very definite reservations must be made with regard to the figures published in the *Report* and those given here in Tables II and III—particularly as to their comparability. To quote the remarks which accompany them in the *Report*: "... it cannot yet be said that all the conditions necessary for their full comparability have been fulfilled. With a disease like diabetes mellitus it may never be possible to achieve absolute comparability of national mortality figures, since there is still too great a margin of uncertainty as to the *underlying role of diabetes in causing death*".

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